



## Clinical trial results:

**A multicenter open label phase II study to evaluate the safety and efficacy of deferasirox in combination with deferoxamine followed by transitioning to deferasirox monotherapy in -thalassemia patients with severe cardiac iron overload**

### Summary

EudraCT number	2009-018091-34
Trial protocol	GR
Global end of trial date	06 June 2014

### Results information

Result version number	v1
This version publication date	13 July 2016
First version publication date	07 August 2015

### Trial information

#### Trial identification

Sponsor protocol code	CICL670AGR02
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01459718
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	06 June 2014
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	06 June 2014
Was the trial ended prematurely?	No

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Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the efficacy of the intensive treatment with deferasirox taken per os once daily (20-40 mg/kg/day) plus the subcutaneous infusion of DFO (40 mg/kg/day) for 3-4 days per week in patients with severe cardiac iron-overload ( $4\text{ms} \leq \text{MRI T2}^* \text{Heart} \leq 10 \text{ ms}$ ) over a period of 24 months of study treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Greece: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	0

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85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

In this open-label, single arm study, 31 participants were screened (1 participant was screened twice with 2 screening numbers; therefore, enrollment number = 32). Of these screened participants, 13 participants were randomized.

### Pre-assignment

Screening details:

This was an open-label, single arm study.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Deferasirox / Deferasirox + Deferoxamine (DFO)
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Arm description:

During Phase A, the induction treatment at entry, participants received Deferasirox -DFO combination. During Phase B, when participants transitioned to less intensive chelation therapy, participants received Deferasirox monotherapy.

Arm type	Experimental
Investigational medicinal product name	Defasirox
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Defasirox: 20-40 mg/kg/day orally, once daily

Investigational medicinal product name	Deferoxamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg/kg/day subcutaneous (sc) infusion, 3-4 days per week

Number of subjects in period 1	Deferasirox / Deferasirox + Deferoxamine (DFO)
Started	13
Safety Analysis Set	13
Completed	10
Not completed	3
Physician decision	1
Adverse event, non-fatal	1

Lost to follow-up	1
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## Baseline characteristics

### Reporting groups

Reporting group title	Deferasirox / Deferasirox + Deferoxamine (DFO)
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Reporting group description:

During Phase A, the induction treatment at entry, participants received Deferasirox -DFO combination. During Phase B, when participants transitioned to less intensive chelation therapy, participants received Deferasirox monotherapy.

Reporting group values	Deferasirox / Deferasirox + Deferoxamine (DFO)	Total	
Number of subjects	13	13	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	13	13	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	32.7		
standard deviation	± 4	-	
Gender, Male/Female			
Units: Participants			
Female	8	8	
Male	5	5	

## End points

### End points reporting groups

Reporting group title	Deferasirox / Deferasirox + Deferoxamine (DFO)
Reporting group description: During Phase A, the induction treatment at entry, participants received Deferasirox -DFO combination. During Phase B, when participants transitioned to less intensive chelation therapy, participants received Deferasirox monotherapy.	

### Primary: Number of patients achieving a complete response (CR)

End point title	Number of patients achieving a complete response (CR) <sup>[1]</sup>
End point description: Complete Response is defined as patients that stop intensive deferasirox -DFO treatment, at any time point during the 24 months of study, based on an improvement in the cardiac Magnetic Resonance Imaging T2 star technique (MRI T2*) value being >10ms, and continue to be treated with deferasirox monotherapy without any further need for reverting back to intensive iron chelation treatment during the 24 months of study.	
End point type	Primary
End point timeframe: 24 months	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: There were no pre-planned analysis for this outcome measure	

End point values	Deferasirox / Deferasirox + Deferoxamine (DFO)			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[2]</sup>			
Units: Not Applicable				
number (not applicable)				

Notes:  
[2] - Study was terminated early. Efficacy was not powered for analysis due to low enrollment.

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of patients achieving a partial response (PR)

End point title	Number of patients achieving a partial response (PR) <sup>[3]</sup>
End point description: Partial Response is defined as patients that stop intensive deferasirox -DFO treatment at any time point during the 24 months study and transition to receive deferasirox monotherapy, but due to a deterioration in cardiac MRI T2* to a value < 10 ms revert back to intensive deferasirox -DFO iron chelation therapy during the 24 months of study.	
End point type	Primary
End point timeframe: 24 months	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no pre-planned analysis for this outcome measure

End point values	Deferasirox / Deferasirox + Deferoxamine (DFO)			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[4]</sup>			
Units: Not Applicable				
number (not applicable)				

Notes:

[4] - Study was terminated early. Efficacy was not powered for analysis due to low enrollment.

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of patients with stable disease (SD)

End point title	Number of patients with stable disease (SD <sup>[5]</sup> )
End point description: Stable Disease is defined as those patients that never achieved an improvement in the cardiac MRI T2* to values >10ms during the 24 months of study.	
End point type	Primary
End point timeframe: 24 months	

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no pre-planned analysis for this outcome measure

End point values	Deferasirox / Deferasirox + Deferoxamine (DFO)			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[6]</sup>			
Units: Not Applicable				
number (not applicable)				

Notes:

[6] - Study was terminated early. Efficacy was not powered for analysis due to low enrollment.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in cardiac iron overload of patients in intensive iron chelation therapy consisting of deferasirox-DFO and after transition to deferasirox monotherapy

End point title	Change from baseline in cardiac iron overload of patients in intensive iron chelation therapy consisting of deferasirox-DFO and after transition to deferasirox monotherapy
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End point description:

Cardiac iron overload was determined by cardiac MRI T2\*. Cardiac iron overload also was measured by the monthly velocity of heart MRI T2\*.

End point type	Secondary
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End point timeframe:

screening, 6, 12, 18, 24 months

End point values	Deferasirox / Deferasirox + Deferoxamine (DFO)			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[7]</sup>			
Units: Not Applicable				
number (not applicable)				

Notes:

[7] - Study was terminated early. Efficacy was not powered for analysis due to low enrollment.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to response

End point title	Time to response
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End point description:

Time to response was defined as the time from baseline when the participant had severe cardiac iron overload to the time when the participant achieved mild/moderate cardiac overload (T2\*>10 ms).

End point type	Secondary
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End point timeframe:

24 months

End point values	Deferasirox / Deferasirox + Deferoxamine (DFO)			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[8]</sup>			
Units: Not Applicable				
number (not applicable)				

Notes:

[8] - Study was terminated early. Efficacy was not powered for analysis due to low enrollment.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in liver iron concentration (LIC)

End point title	Change from baseline in liver iron concentration (LIC)
End point description: Change from baseline in LIC was determined by change in liver MRI T2*.	
End point type	Secondary
End point timeframe: baseline, 6, 12, 18, 24 months	

<b>End point values</b>	Deferasirox / Deferasirox + Deferoxamine (DFO)			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[9]</sup>			
Units: Not Applicable				
number (not applicable)				

Notes:

[9] - Study was terminated early. Efficacy was not powered for analysis due to low enrollment.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in serum ferritin levels and LIC

End point title	Change from baseline in serum ferritin levels and LIC
End point description: Change from baseline was evaluated by the observed changes at 6, 12, 18, 24 months.	
End point type	Secondary
End point timeframe: baseline, 6, 12, 18, 24 months	

<b>End point values</b>	Deferasirox / Deferasirox + Deferoxamine (DFO)			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[10]</sup>			
Units: Not Applicable				
number (not applicable)				

Notes:

[10] - Study was terminated early. Efficacy was not powered for analysis due to low enrollment.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Left Ventricular Ejection Fraction (LVEF)

End point title	Left Ventricular Ejection Fraction (LVEF)
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End point description:

LVEF % was measured by cardiac magnetic resonance (CMR).

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End point type	Secondary
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End point timeframe:

6, 12, 18, 24 months

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End point values	Deferasirox / Deferasirox + Deferoxamine (DFO)			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[11]</sup>			
Units: Not Applicable				
number (not applicable)				

Notes:

[11] - Study was terminated early. Efficacy was not powered for analysis due to low enrollment.

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

### Reporting groups

Reporting group title	Deferasirox
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Reporting group description:

Deferasirox

Serious adverse events	Deferasirox		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 13 (38.46%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiac discomfort			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Lithotripsy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemolysis			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pancreatitis acute			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Deferasirox		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Tooth repair			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Wisdom teeth removal			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Discomfort			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Pyrexia			

subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 8		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Seasonal allergy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	7		
Genital burning sensation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Menstrual disorder			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	5		
Cough			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Dysphonia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory distress			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Paranasal sinus discomfort			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Rhinitis allergic			



subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Investigations Blood pressure increased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)  Muscle contusion subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1  1 / 13 (7.69%) 1		
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)  Atrial fibrillation subjects affected / exposed occurrences (all)  Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1  1 / 13 (7.69%) 1  1 / 13 (7.69%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Facial neuralgia subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Hypotonia subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2  1 / 13 (7.69%) 1  4 / 13 (30.77%) 24  1 / 13 (7.69%) 1		

Sciatica subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 3		
Presyncope subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Syncope subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 2		
Blood and lymphatic system disorders Thrombocytosis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)  Hypoacusis subjects affected / exposed occurrences (all)  Tinnitus subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1  1 / 13 (7.69%) 1  1 / 13 (7.69%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Abdominal distension subjects affected / exposed occurrences (all)  Abdominal discomfort subjects affected / exposed occurrences (all)  Abdominal pain upper subjects affected / exposed occurrences (all)  Constipation	3 / 13 (23.08%) 5  1 / 13 (7.69%) 1  1 / 13 (7.69%) 1  2 / 13 (15.38%) 4		

subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	16		
Abdominal pain lower			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Gastric disorder			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	5		
Back pain			

subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	5		
Bone pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 4		
Viral infection subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 3		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2011	Amendment 1 introduced the following changes: amendment in the Table Contents; amendment in the Sections of Study Rationale, Inclusion/Exclusion Criteria, Primary Objectives, Study Design, Treatment Arms, regarding the range values of cardiac T2*; administrative changes in section of patient treatment; amendment in the Template of Visit Schedule and assessments for the correction of any administrative issues; administrative changes in the Sections of Physical Examination, Weight and Vital Signs for Administrative changes in the Pharmacokinetic Analysis section; administrative changes in chapter for Independent Data Monitoring Board role; administrative changes in the chapter of Database Management and Quality Control; amendment in section Interim Analysis Administrative changes in chapter regarding the SSC has being modified; amendment in the Appendix referring to cardiac and liver MRI for better determination and clarification of the measurements and evaluation method; and numbering of protocol Templates and Diagrams had been updated.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported